Classifying Cannabinoid Extracts

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The United States Food and Drug Administration currently prohibits the addition of CBD to food and dietary supplement products

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Introduction

The globalization of the cannabis industry has been paralleled by the commercialization of novel product formats that provide alternatives to inhalation as the primary method of consumption. Recreational and medical markets contain a variety of product offerings that include edibles, beverages, topicals, capsules, tinctures, and vape pens. Unlike dry plant material that is consumed through smoking or vaporization, these value-add products are formulated with cannabinoid-rich plant extracts and, with the exception of vape pens, intended for oral consumption or topical application. In order to meet the growing demand for extract-based consumable products, extraction and manufacturing verticals have been pressured to optimize yield and reduce cost while increasing the scale of their operations.

This effort has produced a range of extraction technologies that are capable of rendering various types of cannabinoid extracts with unique characteristics that further enable the development of novel cannabinoid-based products. The existing nomenclature system for cannabis extracts was originally developed based on the commercial needs and activity within the illicit market, rather than on science and regulation. As a result, the current taxonomy fails to articulate the relationship and differences between extracts, resulting in confusion among consumers and product developers both inside and outside of the cannabis industry.

For the market to continue to grow efficiently, an updated classification system of extracted products is essential. This updated classification system should be based on a clear delineation between product categories and the variety of methods from which these categories can be derived. At its foundation, the delineation first needs to separate what is “plant material” and what is an “extracted” form of the “plant material” (Figure 1). One clear delineator is if the plant’s cells remain intact or if they are broken open. For example, kief is a product that represents the collection of glandular trichomes, which are cells on the surface of the leaf and flowers that contain concentrated cannabinoids and terpenes. Kief’s “powdery” consistency results from this concentration of whole cells that have broken-off from the surface of the plant tissue but remain intact as a cell-type. When kief is compressed, some rupturing of the cells occurs and the oils, waxes, cellulose, and other internal components to the cell are combined. This causes the product to change from a powdery consistency to a resinous and “putty-like” form referred to as hashish. Like kief, there are many methods to produce hash and many ways to process hash into other products. But the fundamental separation in classification is if the plant cells are broken and the contents released. Prior to this, it is considered plant material, and post this it is now considered an extract.

This review introduces a new classification system for extracts derived from the *Cannabis sativa* plant that addresses differences in extract composition, manufacturing methodology, and regulatory designation. A discussion on cannabinoid chemistry, available technologies for cannabinoid extraction, refinement and synthesis, and issues with extract quality and batch consistency is also provided with the aim of informing product formulators and consumers on the differences in functionality, composition, and safety of cannabinoid extracts so that they can make informed decisions when purchasing extracts and extract-based products.

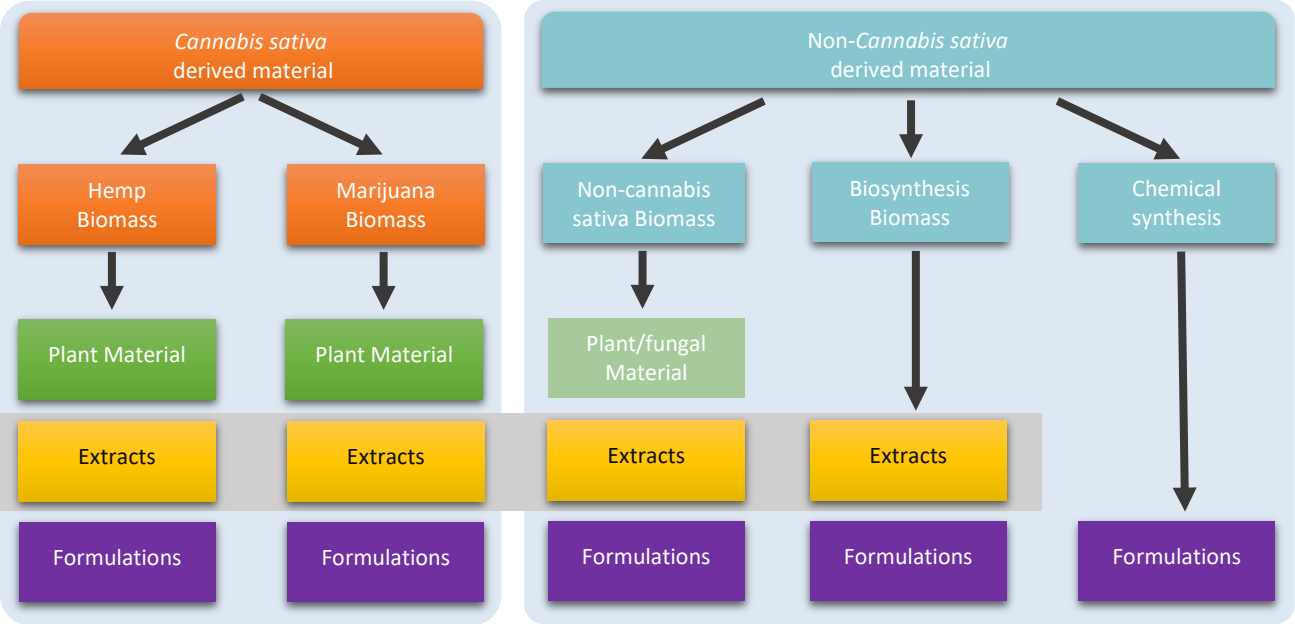


Figure 1: A tree diagram of the source materials and derivatives in the cannabis market. Product lineages are defined as being derived from the plant species *Cannabis Sativa* L. or from some other source. The delineation between Hemp and Marijuana is solely a regulatory definition that may impact the type, format and availability of the derivative product depending on the jurisdiction the product is being produced or sold in.

A New Classification System for Cannabinoid Extracts

Once an extract is produced, the extract can be organized into 3 basic groups with a common subgroup delineation (Table 1). The basic groups include:

Raw Extract - the resulting compliment of the plant cells after they have been broken open. This is often referred to as a "whole plant extract."

Refined Extract – an extract obtained after a process has been applied to the raw extract. This includes a concentration of the raw extract or the removal of a component. For clarity, in the current market vernacular, "Concentrates" and "Distillates" are derived using processes that focus on concentrating the cannabinoid fractions, while "Full spectrum" or "Broad spectrum" extracts are produced by removing undesirable compounds like waxes, terpenes, and in the latter case, reducing the THC content. In this system, they are all grouped as "Refined" and their differences are attributed to the type of extraction and refinement methods used in their production.

Isolates - products with a single component typically generated from raw or refined extracts.

The sub-classification is common across all basic groups and is focused on the presence or absence of a controlled substance in the product. Which cannabinoids, if any, are considered controlled or restricted varies across legal jurisdictions. This is one of the more challenging aspects of the cannabis market as some extracts can contain traces or varying concentrations of controlled substances such as THC. To make things more complicated, the definitions of "containing" a controlled substance are also constantly changing. For example, in jurisdictions such as the United States:

- If a *Cannabis sativa* plant raw extract, refined extract, or isolate contains THC levels equal to or less than 0.3% (w/w), it is considered an unscheduled substance.
- If a *Cannabis sativa* plant raw extract, refined extract, or isolate contains THC levels greater than 0.3% (w/w), it is automatically classified as a controlled substance.

In contrast, in Canada any derivative of the cannabis plant is considered a controlled substance regardless of the THC content. If a buyer of extracts is sourcing from multiple locations, they require a clear designation on levels of controlled substances. Thus, the sub-classification will provide clarity independent of the base extract group.

Class	Sub class	Cannabinoid Potency Range (%w/w)	Terpene Averages (%w/w)	Extract Definition	Previous Designations
Raw	Scheduled	30 – 65%	< 5%	An extraction of the total soluble components of the plant material which includes a controlled substance	Whole-Plant Extract
	Unscheduled	30 – 65%	< 5%	An extraction of the total soluble components of the plant material	
Refined	Scheduled	50 –95%	< 10%	A concentration of a raw plant extract which includes a controlled substance	Full Spectrum, Broad Spectrum, Distillate, Concentrates
	Unscheduled	50 –95%	< 10%	A concentration of a raw plant extract	
Isolate	Scheduled	> 95%	< 0.1%	An isolation of a single compound that is or contains a controlled substance	Isolate
	Unscheduled	> 95%	< 0.1%	An isolation of a single compound	

Table 1: A proposed classification of extracts for the emerging cannabinoid industry.

Understanding Cannabinoid Chemistry and Extraction Science

A variety of processes are employed for the recovery and purification of cannabinoid extracts. Solvent-based extraction processes are generally utilized for the production of commercial-scale extracts, while solvent-less methods are more suitable for craft-style products or smaller volumes. The selection and development of an extraction process should take into account factors such as end use, purity, extraction time, process scalability, and cost constraints.

In many cases, the composition of an extract is characteristic to the type of extraction process employed. Additionally, the chemical profile of an extract can be further tailored by modifying the selectivity of a given extraction process for specific chemical compounds. In this context, a sound understanding of the various constituents of cannabinoid extracts is necessary to properly wield or engineer the functionality of extraction methodology. Formulators seeking to incorporate cannabinoids into finished products should also consider the implications that different extraction processes have on extract purity and composition to ensure that product quality, product safety, and ingredient compatibility are achieved.

Constituents of Cannabis Extracts

Cannabinoids

The cannabis plant is a notoriously heterogenous species containing over 500 unique compounds, many of which possess a range of biological and therapeutic activity[1]. Cannabinoids arguably constitute the most therapeutically valuable class of compounds. To date, 100+ cannabinoids have been identified in the cannabis plant[1,2]. However, most of these cannabinoids are observed in trace amounts. Cannabis plants produce cannabinoids to protect against pathogen infection, insect herbivory and UV damage from sunlight. THC and CBD are frequently referred to as the "major" cannabinoids due to their concentration in the plant. Despite the presence of other "minor" cannabinoids present in lesser quantities often below 1% (w/w), THC and CBD concentrations are commonly utilized as benchmark delineators of different varieties of the cannabis plant and different cannabis-derived products. Interestingly, it is the acidic precursors of these and other cannabinoids that are found in plant material (Table 2). Decarboxylation of the plant material or of the recovered extract is required to convert acidic cannabinoids into their neutral forms.

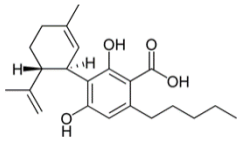
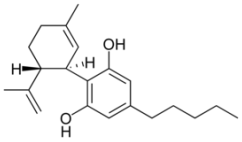
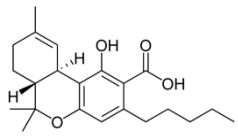
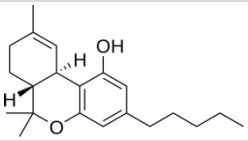
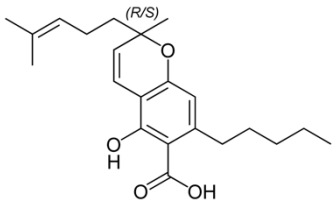
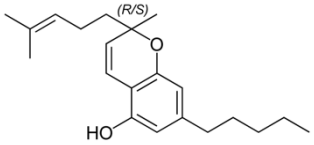
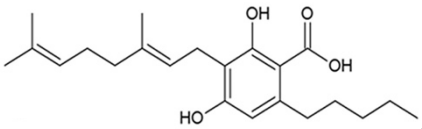
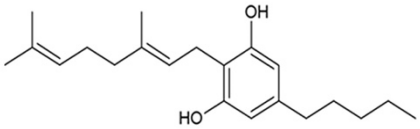
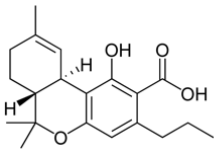
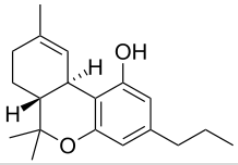
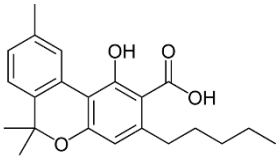
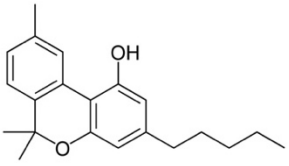
Cannabinoid	Acid Form	Neutral Form
Cannabidiol (CBD)		
Tetrahydrocannabinol (THC)		
Cannabichromene (CBC)		
Cannabigerol (CBG)		
Tetrahydrocannabivarin (THCV)		
Cannabinol (CBN)		

Table 2: Structures of the five most common cannabinoids (acidic and neutral forms).

Marijuana and Hemp are both varieties of the *Cannabis Sativa* L. plant species. A species is a group of organisms that share key traits and can produce offspring of the same type. However, within a species, there can be considerable variability in appearance (for example, a granny smith apple and red delicious apple are both part of the *Malus domestica* species). In the case of *Cannabis sativa* L., the cannabinoid profile and content vary between marijuana and hemp varieties. These differences have formed the foundation of regulatory definitions applied to distinguish between marijuana and hemp. As mentioned, in the United States, *Cannabis sativa* plant tissue or processed material containing THC levels equal to or less than 0.3% (w/w) are classified as hemp, while plant tissue or processed material containing THC levels greater than 0.3% (w/w) are classified as marijuana.

In the context of cannabinoid extractions, hemp varieties are usually cultivated for CBD, while marijuana varieties are often cultivated for THC. That being said, certain marijuana varieties may also produce appreciable amount of CBD. For example, hemp in the United States often contain CBD concentrations in excess of 10% (w/w), and therefore are farmed as a primary source of CBD. In comparison, in Canada where regulated hemp varieties contain between 1.5 – 3% (w/w), hemp is not considered to be a commercially viable plant source of CBD.

In chemical terms, cannabinoids are considered terpeno-phenolics, meaning that the molecule has a terpene structure coupled to a phenolic compound. Using cannabidiolic acid (CBDa) as an example, the molecule can be broken down into a limonene moiety (a terpene) connected to an olivetolic acid group (Figure 2). From a pure chemical synthesis approach, such molecules are created using reactive precursors of the two components.

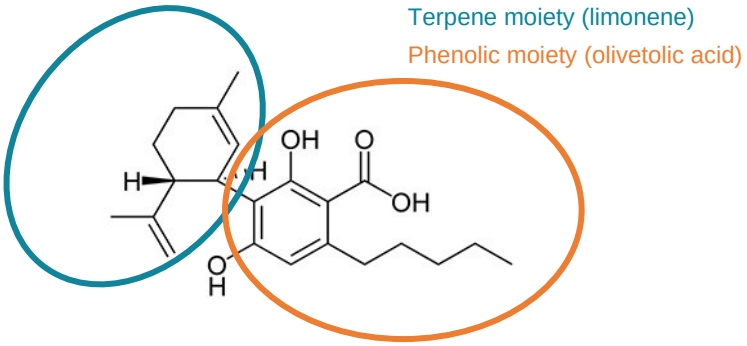


Figure 2: The terpeno-phenolic structure of cannabidiolic acid (CBDa).

Terpenes

Terpenes comprise the largest class of compounds present in the *Cannabis Sativa* L. “Terpenes” is a broad term that encompasses hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), and diterpenes (C20) compounds, all of which can be contrasted by the number of isoprene units present in the molecule (Table 3). The smaller hemi and monoterpene molecules are often classified as light terpenes due to their low vapour pressure, which ultimately renders them highly volatile and prone to evaporation under elevated temperatures. In comparison, the sesquiterpenes are less volatile and thus described as heavy terpenes. Over 120 different terpenes have been identified in the cannabis plant to date, most of which are lipophilic (tending to combine with or dissolve in lipids or fats) in nature[3].

In addition to providing protective insecticidal properties to the plant, terpenes are also responsible for the taste and smell of the cannabis plant and its extracts. Most notably, it has been suggested that terpenes influence THC's receptor activity through a variety of mechanisms, and that they display significant activity at serotonin 5-HT1A and 5-HT2a receptors which may synergistically enhance the analgesic and mood effects associated with cannabinoid use[4,5]. Under this premise, the "entourage effect" stipulates that cannabinoids, terpenes, and other plant compounds interact synergistically to provide superior efficacy compared to refined isolates or singular components of cannabinoid extracts[4]. This further emphasises the importance of understanding the impact of decarboxylation or extraction processes on extract composition, particularly in the context of batch consistency and efficacy for medical applications.

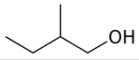
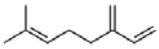
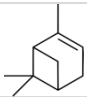
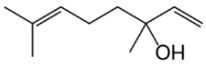
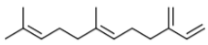
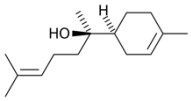
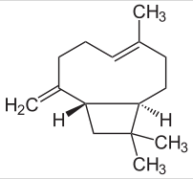
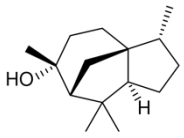
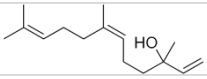
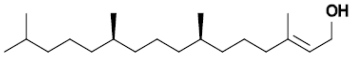
Terpene and Flavonoids Class		Example	Structure
Hemiterpene (C5)	Alicyclic Hemiterpenoid	Methyl butenol	
Monoterpene (C10)	Alicyclic Monoterpene	Myrcene	
	Monocyclic Monoterpene	Limonene	
	Bicyclic Monoterpene	Pinene	
	Alicyclic Monoterpenoid	Linalool	
Sesquiterpene (C15)	Alicyclic Sesquiterpene	β-Farnesene	
	Monocyclic Sesquiterpenoid	Bisabolol	
	Bicyclic Sesquiterpene	β-Caryophyllene	
	Tricyclic Sesquiterpenoid	β-Cedrol	
	Alicyclic Sesquiterpenoid	Nerolidol	
Diterpenoids (C20)	Alicyclic Diterpenoid	Phytol	

Table 3: Structures of common hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), and diterpenes (C20) found in cannabis plants.

Flavonoids

Similar to other plant species, the cannabis plant and its extracts contain flavonoids, which are classified as secondary polyphenolic metabolites. Within the plant kingdom, flavonoids support a range of essential functions including pollination, plant development, cellular signalling and enzyme activity, as well as defense against environmental aggressors such as bacteria and UV exposure[6,7]. While most flavonoids display as yellowish pigments, they can be divided into four main groups: flavonoids, isoflavonoids, neoflavonoids and anthocyanins.

Cannabis-derived flavonoids are labelled using the portmanteau “cannaflavins”. To date, two cannaflavins have been identified and classified creatively as cannaflavin-A, and cannaflavin-B with the most distinguishing feature being the length of the isoprene tail. Cannaflavin-A and B were isolated during the 1980’s by Dr Barrett and her team. The realization that cannaflavins A and B, which are biosynthesized by prenylation of chrysoeriol, are in vitro inhibitors of prostaglandin E2 production prompted further exploration into their use as anti-inflammatory agents[8,9,10]. In this endeavour, it was reported that cannaflavin-A proved to be 30 times more effective than aspirin in studies[8]. Cannaflavin-B, which was more recently isolated in 2013, requires further research to investigate and determine its potential medicinal value.

While dietary flavonoids consumed from fruits and vegetables are touted for their anti-inflammatory, antioxidant, and anti-cancer effects, certain flavonoids may also modulate drug absorption through CYP450 enzyme mediation[7,11,12]. For instance, naringenin is a flavonoid present in grapefruit and is a known inhibitor of the CYP3A4 enzyme family[13]. As thus, certain drugs metabolized by CYP3A4 enzymes contain warnings against consuming grapefruit products since the inhibition of these enzymes caused by naringenin and other compounds will result in reduced metabolism and elevated serum levels of the drug in question. Interestingly, CYP3A4 plays a critical role in the metabolism of THC and CBD[14-16]. In this context, the therapeutic benefits and modulatory effects of the cannaflavins remains intriguing and likely warrants further investigation.

Minor Plant Constituents

The cannabis plant also contains epicuticular waxes, which are comprised of complex mixtures of very-long-chain (VLC) aliphatic compounds and their oxygenated derivatives, including fatty acids, alkanes, alcohols, esters, aldehydes, ketones, and triterpenes. These waxes are primarily present on the surface of plant leaves and act as a water-proofing agent and the first line barrier defense against pests. The medicinal benefit of these compounds remains undetermined. However, plant waxes are often used in cosmetics and food applications as oil-binding or viscosity enhancing agents. Other minor components present in the cannabis plant include nitrogenous compounds, amino acids, various proteins and glycoproteins, enzymes, sugars, hydrocarbons, simple alcohols, simple aldehydes, simple ketones, and fatty acids. While the functionality of chemical classes falls outside the scope of this discussion, they further demonstrate the diversity of the cannabis plant and its extracts.

Variability in Plant and Extract Composition

While the composition of an extract is indeed a function of the type of extraction process employed, there are other considerations that should be taken into account when optimizing manufacturing processes to achieve batch consistency and process reproducibility. For example, one consideration is the composition of the starting plant material.

Cannabis sativa is a dioecious sexually reproducing organism (a single plant is either male or female) and follows the botanical sub-species delineations of variety or cultivar. If the variation was created by human intervention, it is referred to as a cultivated variety or "cultivar". Research on cannabis evolution has revealed a convoluted history as to its origin and species definition. However, the current consensus is that the species is *Cannabis sativa* L., and the subspecies variation that we currently see in the cannabis industry—designations such as sativa, indica, ruderalis, and the extensive commercial lineages—are examples of either varieties or cultivars.

Commercial lineages, which often feature creative names such as "Pink Kush" and "Headband" in the recreational markets, suggest discrete and consistent differences in cannabinoid and terpene profiles between different subspecies varietals. However, there is wide variability inherent to growing large numbers of plants, more commonly referred to as "crop production systems" in agriculture-speak. Cannabis crop production systems currently include outdoor field production, indoor production under artificial lights with soil or artificial growth media, as well as greenhouse production. Cannabinoid and terpene levels fluctuate with environmental conditions, and thus, a particular cannabis varietal planted in the field can fluctuate between the legal designation as hemp (less than 0.3% (w/w) THC) or marijuana (greater than 3% (w/w) THC) or vary in cannabinoid and terpene profile even within the same lineage. Generally speaking, this degree of variation increases from indoor production to greenhouse production, and to outdoor field production.

Within the same production system, plant profiles are also influenced by various cultivation conditions, such as fertilizer or soil chemistry, light intensity and exposure time, and temperature. Such parameters are often characteristic to the location of crop production. For instance, the soil composition and temperature characteristic to an outdoor cultivation site in Southern California will be different than the outdoor cultivation conditions found in Colombia or the Canadian prairie provinces. Inadvertently, a Pink Kush varietal produced in each of these areas will possess different cannabinoid and terpene profiles.

Additionally, contaminants may be inherently introduced during cultivation process. Common contaminants include microbes such as yeasts and molds, heavy metals leached from the surrounding soil, and pesticides that are introduced during the growth cycle. Certain downstream processes can be utilized to reduce the bioburden or impurity levels present in cannabis extracts, whereas biosynthetically or chemically synthesized cannabinoids are devoid of these contaminants.

The Chemical Composition of Various Plant Extracts

The objective of any extraction process is to recover the bioactive-rich trichomes, which are glandular hair-like structures found on the surface of plants. The main purpose of these structures is insect defense and environmental protection, whereby in the latter case they can act to reduce water evaporation from the leaf and prevent frost from damaging the leaf surfaces. Visually, trichomes appear as small hairs that protrude from the surface of the cannabis plant's flowering heads and the surrounding leaves. Trichome recovery can be achieved using a variety of techniques that are broadly classified as solvent-based or solvent-less. In many cases, additional downstream processing is required to remove unwanted impurities or to concentrate the profile of desired actives, which include not only the cannabinoids and terpenes, but also a plethora of other lesser known but equally important compounds such as flavonoids, phenolics, and sterols (Figure 3).

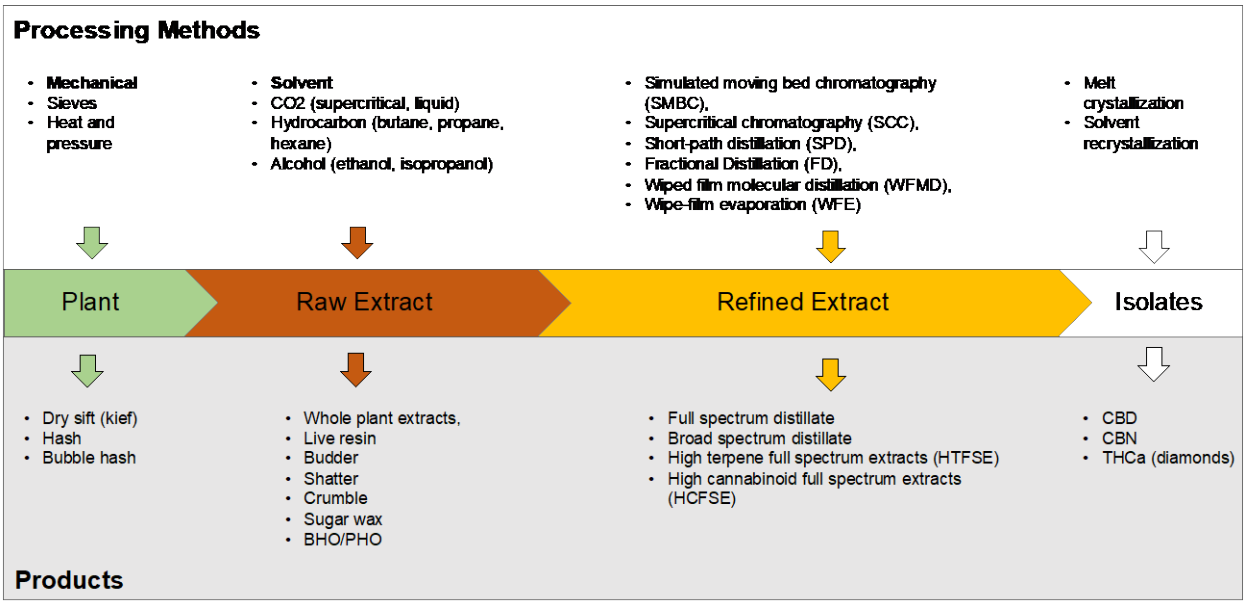


Figure 3: An overview of extraction and refinement methods used to manufacture cannabis plant derivatives, raw extracts, refined extracts, and isolates.

The existing nomenclature system for cannabis extracts was originally developed based on the commercial needs and activity within the illicit market, rather than on science and regulation. As a result, the current taxonomy fails to articulate the relationship and differences between extracts, resulting in confusion among consumers and product developers outside of the cannabis industry. For example, the term “Broad Spectrum” does not indicate that these extracts characteristically contain less than 0.3% w/w THC. Similarly, “Full-Spectrum” fails to confer that these extracts are obtained by winterizing “Whole Plant” extracts to remove the unwanted waxes.

To resolve this confusion, we have proposed a new taxonomy (detailed above in Table 1) that aims to identify and organize extract lineage and further subcategorize extracts as Scheduled or Unscheduled based on the presence of controlled substances as defined by specific regional market regulations. Under this system, extracts can be classified as Raw (the resulting compliment of the plant cells after they have been broken open), Refined (a raw extract that has been processed to remove unwanted compounds or concentrate actives), and Isolates (extracts containing a singular component at concentrations greater than 95% (w/w). A review of this new naming system as it pertains to the existing classification system is provided below.

Raw Extracts

Raw extracts encompass all solvent-based extractions, including those produced using oxygenates (alcohols, ethers, esters, etc.), hydrocarbons (propane, butane, hexane), and various phases of carbon dioxide (Figure 4). Examples include whole plant extracts and live resin, the latter of which in all intent and purpose is likely the most representative extract of the whole plant obtained from freshly harvested cannabis that is flash frozen and cold extracted with a light hydrocarbon, and as thus includes both aqueous and hydrophobic factions of the plant material. These extracts contain the full suite of bioactive molecules, as well as the waxes and fatty alcohol components of the epicuticular matrix, and long-chain

degradation products of chlorophyll. The heterogeneous and compositionally complex composition of raw extracts varies with the type of solvent used due to unique differences in solvent-specific solubility.

Refined Extracts

Refined extracts are produced by refining a raw extract to remove unwanted compounds or recover plant actives. Examples of refined extracts include full-spectrum extracts, broad-spectrum extracts, distillates, and concentrates such as shatter (Figure 4). Under the current nomenclature system, a full-spectrum extract contains the entire profile of solvent extractable compounds originally present in the plant. A full-spectrum extract ultimately preserves the natural ratios of compounds within the cannabis plant tissue while removing impurities that to current knowledge do not added value or compromise the quality and physiochemical properties of the extract, such as waxes and other lipids.

Waxes are commonly removed using a process known as winterization, which utilizes a solvent such as ethanol to dissolve the extract. This solution is cooled to sub-zero temperatures (typically –20°C) and held for 12-24 hours. During this time, the waxes become insoluble under these conditions and begin to precipitate out. This mixture is then cold-filtered and the clarified filtrate goes on to a solvent removal stage to yield the de-waxed extract. As an example, shatter is a hydrocarbon extract that is nearly devoid of waxes and characterized as a thin amorphous solidified resin that is produced by controlling the rate of solvent removal. Unlike cannabis concentrate variations such as bubble hash, dry sift, and rosin, which include the lipid plant components, full-spectrum extracts remove these elements and leave behind only what is believed to be therapeutically desired to deliver an entourage effect.

Broad-spectrum extracts are a refined version of the full-spectrum class described above; they contain a range of cannabinoids and all the other compounds (excluding waxes) within the plant except THC, which is removed to levels below a set threshold after the initial extraction using downstream processing methods such as chromatography. Since broad-spectrum extracts contain multiple cannabinoids, they also produce a form of the entourage effect, but in an altered form due to the absence of THC.

Distillate products are considered concentrates due to their elevated cannabinoid levels. They are highly refined using various chemical and thermal processes to concentrate the cannabinoid components. The correct choice of the primary extraction process, typically some form of solvent extraction, can significantly simplify refinement. Short-path distillation (SPD) and wiped-film molecular distillation (WFMD) are commonly applied refinement processes that employ high vacuum to facilitate non-destructive separation of thermally sensitive compounds. The distillation techniques described separate compounds from each other based on their boiling points. This technique has gained popularity because the boiling points of the compounds fall into groupings, such as the high boiling point cannabinoids, followed by the sesquiterpenes, and monoterpenes. Higher boiling point compounds such as pigments and triterpenes are left over in the remaining depleted resin fraction.

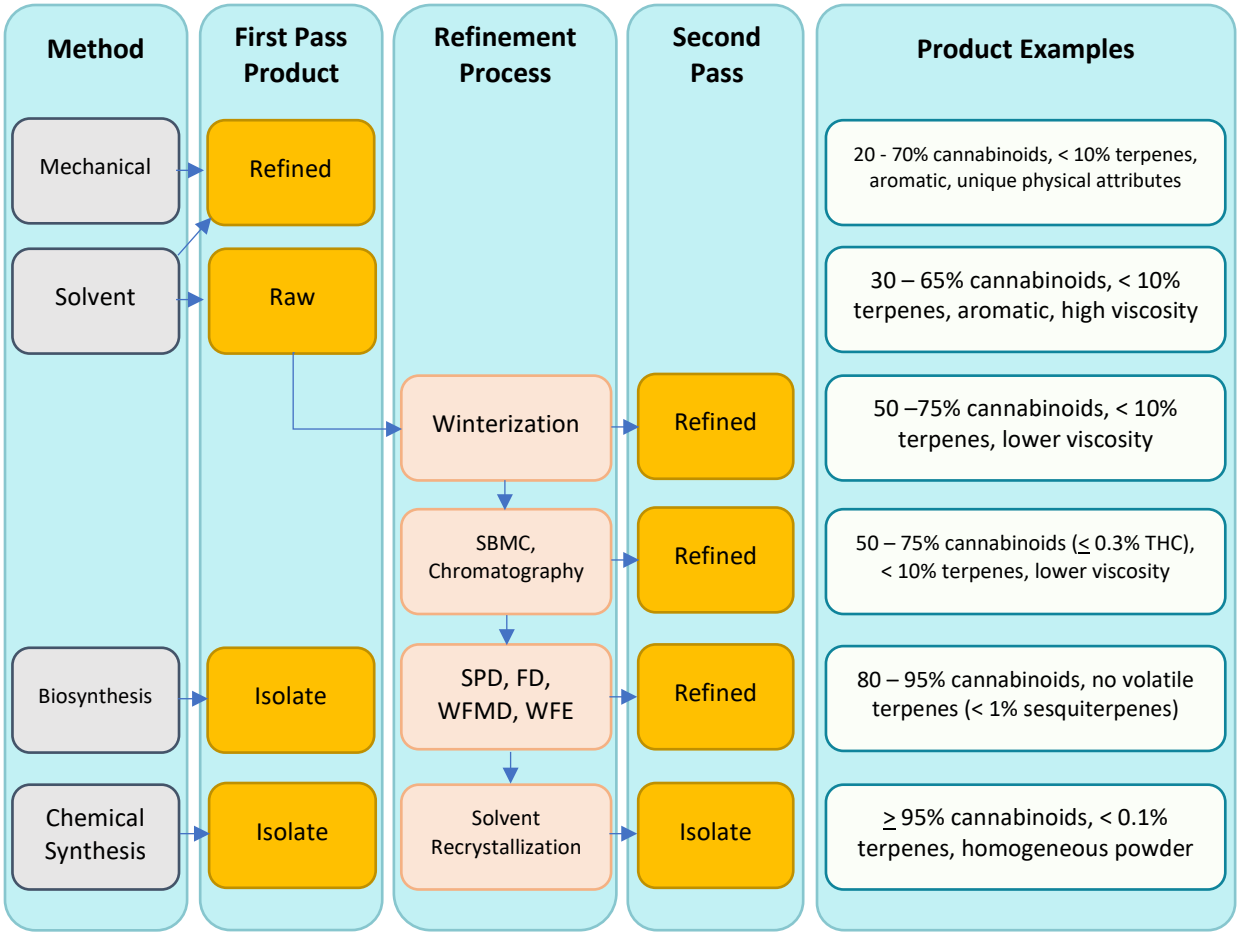


Figure 4: Flow process of the various cannabinoid synthesis, extraction, and refinement methods available for the production of raw extracts, refined extracts, and isolates (SBMC = Simulated Moving Bed Chromatography, SPD = Short Path Distillation, FD = Fractional Distillation, WFMD = Wiped Film Molecular Distillation, WFE = Wiped Film Evaporation)

Isolates

Isolates are the most concentrated form of cannabis extract products and feature a single cannabinoid often at concentrations greater than 95% (w/w), with many commercially available isolates today approaching 99% (w/w). In general practice, isolates are produced by taking distillate (refined extract) and processing it further (Figure 4). If the cannabinoid can be crystalized, an appropriate solvent mixture is used to drive the crystallization process. An alternative method for compounds that do not readily crystallize involves using chromatography to separate highly pure fractions.

Due to the absence of other cannabinoids and bio-actives, isolates do not impart any entourage effects. Rather, the properties of an isolate are derived solely from the single cannabinoids constituting its composition. Plant-derived isolates require significant downstream processing to remove all other plant constituents, and yet in the case of the easily extracted major cannabinoids CBD and THC, they may demand a lower price than refined extracts (full-spectrum or broad-spectrum extracts) due to their perceived lack of therapeutic value. However, isolates offer significant formulation advantages in the context of batch consistency, ease of handling due to their free-flowing powder-like form at room temperature, as well as ease of formulation and improved stability due to the absence of impurities and

volatile terpenes. Isolates may be combined with other extracts to fortify their potency or to recreate whole-plant or full-spectrum (raw) formulations. Unfortunately, their utility in recreating raw extracts remains limited by analytics and the current scientific understanding of the therapeutic significance of the other hundreds of compounds present in the cannabis plant.

Synthesized Cannabinoid Isolates

Isolates may also be chemically synthesized or produced using biosynthetic approaches. These technologies have the potential to overcome the quality and batch consistency issues that inadvertently plague cannabinoid extracts. In particular, biosynthesis offers the advantage of scalable manufacturing of high purity isolates that are devoid of common contaminants introduced during agricultural style cultivation, such as pesticides, microbes, and heavy metals. Biosynthesis utilizes a defined starting material as the microorganism hydrocarbon source that is fed into the concentration and purification unit operations. Consequentially, this reduces the processing complexity and improves the quality, consistency, sustainability, and cost effectiveness of the final product. While the optimization of biosynthetic technologies has the potential to offer a new grade of highly pure cannabinoid ingredients, this technology is also the solution to enabling the commercialization of the minor cannabinoids, which currently remain unavailable in appreciable quantities from plant sources.

In comparison, chemical synthesis is regarded as an efficient and highly scalable process with the primary obstacle being the requirement for precursor molecules which may themselves be bio-derived or extremely costly to produce. Additionally, the feasibility of this approach is limited by the high cost associated with the entire unit of operations required to recover and refine isolates, which is why (in addition to regulatory distinctions between plant-derived and synthetic cannabinoids) this particular method has not been widely commercialized or adopted to date in the field of cannabinoid production.

Solventless Plant Derivatives and Extracts

Solventless extracts such as Kief, Bubble Hash, and Rosin contain levels of cannabinoids comparable to refined (full and broad-spectrum) extracts. Rather than being chemically extracted from the plant material, these high-potency products are produced using non-solvent based methods that utilize means of mechanically separating the trichomes from the plant material. Kief is a collection of trichome glands that are separated from dried cannabis leaves using a mesh. In this process, the plant material is agitated to encourage separation between the trichomes and the leaves. Due to their size, the trichomes can passthrough a mesh screen and are thus isolated from the plant material. Bubble hash is produced using a similar mesh process. By agitating plant material in an ice water bath, the ice mechanically detaches the trichomes from the flower and leaves. The trichomes pass through the mesh screens and are collected as a paste and dried. Rosin is produced by placing wet or dried cannabis leaves or Kief (trichomes) between two sheets of heat-resistant, anti-stick material, such as thin mylar. Heat and pressure are applied to the pressure plates, causing the trichomes to melt and flow out the sides of the plates for collection.

Harnessing the Full Potential of Cannabinoid Extracts Requires a New Naming System

The current naming convention for cannabis plant extracts fails to clearly delineate between the various product categories and the methods from which they are derived. Classifying extracts as “Raw”, “Refined” or “Isolates” provides improved insights into the process lineage of different extracts and allows them to

be further classified as “controlled” or “uncontrolled” according to a sub-classification common across all basic groups that focuses on the presence or absence of a controlled substance, such as THC, based on the regional market of sale. This new naming convention provides a robust solution to classifying extracts based on their composition, manufacturing methods, and regulatory status.

Considering the number of extraction and refinement technologies that have been developed for the purposes of manufacturing various cannabinoid extracts, it is important to note that the method of extraction contributes to the extracts’ chemical composition and, by extension, its pharmacological effects. In this context, the chemical composition of an extract is a fingerprint of not only the unique cannabis varietal used as starting material, but also of the employed extraction method. Therefore, the intentional design of a cannabinoid extract is contingent on a sound understanding of the limitations of each extraction method and the solvent’s selectivity for specific compounds. While this information will inform the properties of the recovered cannabinoid material, it is also essential for selecting appropriate post-extraction processing methods to either remove unwanted compounds (including those imparted by the extraction process on the cannabinoid extract, such as solvents) or to selectively recover and isolate the desired actives. Failure to understand or consider these parameters greatly limits the efficiency, consistency, and quality of the final extract product.

These considerations should also be taken into account by formulators seeking to integrate cannabinoid ingredients into various consumer products to ensure that ingredient compatibility, product quality, and product stability are achieved. For instance, beverage formulators may consider that the volatility of terpenes and presence of waxes in raw extracts presents a formulation challenge that requires improved emulsification and bitter-masking agents to render a palatable and shelf-stable product. Similarly, pharmaceutical formulators may be wary of residual solvents and other impurities that impact the purity and safety profile of the final product. Nutraceutical formulators, cosmetic scientists, and food formulators may take into account chemical and microbial contaminants that present health risks. By and large, understanding the type of extraction process utilized in the manufacturing of a cannabinoid extract enables formulators to better assess the composition, quality, and safety of the extract and make an informed determination of its suitability for commercial formulation.

As discussed, biosynthetic and chemical synthesis of cannabinoids may offer a solution to the quality and batch consistency issues that formulators face with plant-derived cannabinoid extracts. Biosynthesis is particularly well-suited to overcome these challenges due to the scalability of this approach and provide high-purity cannabinoid ingredients at an affordable price that facilitates their use in commercial and medical products[17]. Perhaps most notably, biosynthesis has the potential to enable the commercial availability of minor cannabinoid isolates which are currently unattainable due to the low concentrations of these compounds within the starting plant material that renders their extraction economically unfeasible. In this light, biosynthesis will provide a means of standardizing cannabinoid extracts, recreating plant-derived cannabinoid profiles, and perhaps most importantly, engineering new profiles with specific clinical utility.

In the interim, the industry stands to gain from adopting the proposed new naming convention given the clarity that it will provide consumers, brands, and regulators on the differences between cannabinoid extracts. While the new designation distinguishes between extract composition, manufacturing processes, and regulatory designation, it is also accommodating of both existing extract products and those that may be realized in the future due to advancements in cannabinoid processing and synthesis technologies. The

clarity provided by this robust classification system will help to further the adoption of cannabinoid products, particularly among sectors encumbered by unfamiliarity with the cannabinoid landscape.

LAVVAN's Cannabinoid Solutions

At the forefront of cannabinoid cellular agriculture, LAVVAN utilizes yeast fermentation technology to produce high-quality, reliably sourced, natural cannabinoid ingredients[38]. LAVVAN will provide cannabinoids with unparalleled purity, consistency, potency, and sustainability at a scale capable of serving a range of industries including health, beauty, food and beverage, and pharmaceuticals. LAVVAN's cannabinoids are identical to those found in nature and produced in a cGMP facility in accordance with the most stringent standards, including being devoid of pesticides, mold, bacteria, and other contaminants often found in traditional cannabis agriculture. In addition to providing high purity cannabinoid ingredients, LAVVAN will leverage its cannabinoid formulations expertise to support its industry partners with integrating cannabinoids into formulations for various end products that require specific utility.

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